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(54) **PULSATILE RELEASE HISTAMINE H2 ANTAGONIST DOSAGE FORM**

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(56) **References Cited**

U.S. PATENT DOCUMENTS

4,248,857	A	2/1981	DeNeale et al.	
4,728,512	A	3/1988	Mehta et al.	
4,851,229	A	7/1989	Magruder et al.	
4,863,742	A	9/1989	Panoz et al.	
4,871,549	A	10/1989	Ueda et al.	
4,894,240	A	1/1990	Geoghegan et al.	
4,915,949	A *	4/1990	Wong et al.	424/438
4,983,401	A	1/1991	Eichel et al.	
5,011,692	A	4/1991	Fujioka et al.	
5,017,381	A	5/1991	Maruyama et al.	

(List continued on next page.)

FOREIGN PATENT DOCUMENTS

EP	0239361	9/1987
EP	0391518	10/1990
EP	0431877	6/1991
EP	1010423	6/2000
WO	92/10173	6/1992
WO	00/25752	5/2000
WO	00/42998	7/2000
WO	01/13898	3/2001

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(57) **ABSTRACT**

A unit dosage form, such as a capsule or the like, for delivering drugs into the body in a circadian release fashion comprising one or more populations of drug-containing particles (beads, pellets, granules, etc.) is disclosed. Each bead population exhibits a pre-designed rapid or sustained release profile with or without a predetermined lag time of 3 to 5 hours. Such a circadian rhythm release drug delivery system is designed to provide a plasma concentration-time profile, which varies according to physiological need at different times during the dosing period, i.e., mimicking the circadian rhythm and severity/manifestation of gastric acid secretion (and/or midnight gerd), predicted based on pharmaco-kinetic and pharmaco-dynamic considerations and in vitro/in vivo correlations.

46 Claims, 5 Drawing Sheets

Circadian Variations in Gastric Acid Secretion